	From the INTERNATIONAL BUREAU			
PCT	То:			
NOTIFICATION OF THE RECORDING OF A CHANGE  (PCT Rule 92bis.1 and Administrative Instructions, Section 422)  Date of mailing (day/month/year) 04 April 2001 (04.04.01)	WIBBELMANN, Jobst Wuesthoff & Wuesthoff Schweigerstrasse 2 D-81541 München ALLEMAGNE			
Applicant's or agent's file reference				
EP-83244/PCT	IMPORTANT NOTIFICATION			
International application No. PCT/EP99/06830	International filing date (day/month/year) 15 September 1999 (15.09.99)			
The following indications appeared on record concerning:      The applicant the inventor	the agent the common representative			
Name and Address	State of Nationality State of Residence DE DE			
GOLDHAM BIOGLAN PHARMA GMBH Am Wasserberg 11 D-86441 Zusmarshausen Germany	Telephone No.			
Germany	Facsimile No.			
	Teleprinter No.			
The International Bureau hereby notifies the applicant that the X the person X the name X the additional that the x				
Name and Address	State of Nationality State of Residence			
OMNIA PHARMA S.R.L. Via Fiume Giallo 228 I-00144 Roma	Telephone No.			
Italy	Facsimile No.			
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
X the receiving Office	the designated Offices concerned			
the International Searching Authority	X the elected Offices concerned			
the International Preliminary Examining Authority	other:			
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Céline Faust			
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38			

A Company of the second	From the INTERNATIONAL BUREAU				
PCT  NOTIFICATION OF ELECTION  (PCT Rule 61.2)  Date of mailing (day/month/year) 12 May 2000 (12.05.00)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE  in its capacity as elected Office				
International application No. PCT/EP99/06830	Applicant's or agent's file reference EP-83244/PCT				
International filing date (day/month/year) 15 September 1999 (15.09.99)	Priority date (day/month/year) 16 September 1998 (16.09.98)				
Applicant FRANK, Artur et al					
X in the demand filed with the International Preliminary  10 April 2000 (  in a notice effecting later election filed with the Intern	(10.04.00)				
2. The election X was was not made before the expiration of 19 months from the priority of Rule 32.2(b).	date or, where Rule 32 applies, within the time limit under				
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Nestor Santesso				

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

	From the INTERNATIONAL BUREAU				
PCT	То:				
NOTIFICATION OF THE RECORDING OF A CHANGE  (PCT Rule 92bis.1 and Administrative Instructions, Section 422)  Date of mailing (day/month/year)	WIBBELMANN, Jobst Wuesthoff & Wuesthoff Schweigerstrasse 2 D-81541 München ALLEMAGNE				
25*May 2000 (25.05.00)					
Applicant's or agent's file reference EP-83244/PCT	IMPORTANT NOTIFICATION				
International application No. PCT/EP99/06830	International filing date (day/month/year) 15 September 1999 (15.09.99)				
The following indications appeared on record concerning:      X the applicant      X the inventor	the agent the common representative				
Name and Address GIANETTINO, Andreina Via Francesco Sapori, 49 I-00143 Roma	State of Nationality State of Residence IT IT Telephone No.				
Italy	Facsimile No.				
	Teleprinter No.				
The International Bureau hereby notifies the applicant that the the person      The name      the person					
Name and Address	State of Nationality State of Residence				
GIANNETTINO, Andreina Via Francesco Sapori, 49 I-00143 Roma	IT IT Telephone No.				
Italy	Facsimile No.				
	Teleprinter No.				
3. Further observations, if necessary:					
4. A copy of this notification has been sent to:					
X the receiving Office	the designated Offices concerned				
the International Searching Authority	X the elected Offices concerned				
X the International Preliminary Examining Authority	other:				
	Authorized officer				
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	A. Karkachi				
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38				

	From the INTERNATIONAL BUREAU				
PCT	То:				
NOTIFICATION OF THE RECORDING OF A CHANGE  (PCT Rule 92bis.1 and Administrative Instructions, Section 422)  Date of mailing (day/month/year) 13 March 2001 (13.03.01)	WIBBELMANN, Jobst Wuesthoff & Wuesthoff Schweigerstrasse 2 D-81541 München ALLEMAGNE				
Applicant's or agent's file reference EP-83244/PCT	IMPORTANT NOTIFICATION				
International application No. PCT/EP99/06830	International filing date (day/month/year) 15 September 1999 (15.09.99)				
The following indications appeared on record concerning:      The applicant the inventor	the agent the common representative .				
Name and Address GOLDHAM BIOGLAN PHARMA GMBH Am Wasserberg 11 D-86441 Zusmarshausen Germany	State of Nationality State of Residence DE DE Telephone No.  Facsimile No.				
	Teleprinter No.				
2. The International Bureau hereby notifies the applicant that the X the person X the name X the add	[7]				
Name and Address OMNIA PHARMA S.R.L. Via Fiume Giallo 228 I-00143 Roma Italy	State of Nationality State of Residence IT IT Telephone No.				
,	Facsimite No.				
	Teleprinter No.				
3. Further observations, if necessary:					
4. A copy of this notification has been sent to:					
X the receiving Office	the designated Offices concerned				
the International Searching Authority  the International Preliminary Examining Authority	X the elected Offices concerned other:				
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Dorothée Mülhausen				
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38				

	From the INTERNATIONAL BUREAU				
PCT	То:				
NOTIFICATION OF THE RECORDING OF A CHANGE  (PCT Rule 92bis.1 and Administrative Instructions, Section 422)  Date of mailing (day/month/year) 13 March 2001 (13.03.01)	WIBBELMANN, Jobst Wuesthoff & Wuesthoff Schweigerstrasse 2 D-81541 München ALLEMAGNE				
Applicant's or agent's file reference		IMPOR	RTANT NOTIF	ICATION	
EP-83244/PCT		IIVIFOR	TIANT NOTE	ICATION	
International application No. PCT/EP99/06830		_	e (day/month/ye 1999 (15.09.9		
The following indications appeared on record concerning:      X the applicant      X the inventor	the agen	: [	the commo	n representative	
Name and Address		State of Na	ationality	State of Residence	
GIANNETTINO, Andreina Via Francesco Sapori, 49		IT		IT	
I-00143 Roma		Telephone	No.		
Italy		Facsimile f	No.		
	ĺ	Teleprinter	r No.		
2. The International Bureau hereby notifies the applicant that the the person the name X the add		change has the nati		oncerning: the residence	
the person the name X the add	iless [			State of Residence	
Name and Address		State of Na	ationality	State of Residence	
GIANNETTINO, Andreina Via Fiume Giallo 228		Telephone	No.		
I-00143 Roma Italy					
		Facsimile	No.		
		Teleprinte	r No		
	(Cicpinitor 146)				
3. Further observations, if necessary:				<del></del>	
4. A copy of this notification has been sent to:	Г	<b>-</b>			
X the receiving Office	[	=	signated Offices		
the International Searching Authority	Į	=	cted Offices con	cernea	
the International Preliminary Examining Authority	<u> </u>	other:			
The International Bureau of WIPO	Authorized	officer			
34, chemin des Colombettes 1211 Geneva 20, Switzerland			Dorothée Mü	Ihausen	
Faccimile No.: (41, 22), 740, 14, 25	Telephono	No · (41-22)	338 83 38		

# 14550

# PATENT COOPERATION TREATY

	From the INTERNATIONAL BUREAU			
PCT	То:			
NOTIFICATION OF THE RECORDING OF A CHANGE  (PCT Rule 92bis.1 and Administrative Instructions, Section 422)  Date of mailing (day/month/year) 04 April 2001 (04.04.01)	WIBBELMANN, Jobst Wuesthoff & Wuesthoff Schweigerstrasse 2 D-81541 München ALLEMAGNE			
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EP-83244/PCT				
International application No. PCT/EP99/06830	International filing date (day/month/year) 15 September 1999 (15.09.99)			
The following indications appeared on record concerning:      X the applicant      X the inventor	the agent the common representative			
Name and Address	State of Nationality State of Residence			
GIANNETTINO, Andreina Via Francesco Sapori, 49 I-00143 Roma	Telephone No.			
Italy	Facsimile No.			
	Teleprinter No.			
2. The International Bureau hereby notifies the applicant that the	he following change has been recorded concerning:			
the person the name X the add	dress the nationality the residence			
Name and Address	State of Nationality State of Residence			
GIANNETTINO, Andreina Via Fiume Giallo 228 I-00143 Roma	Telephone No.			
Italy	Facsimile No.			
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
X the receiving Office	the designated Offices concerned			
the International Searching Authority	X the elected Offices concerned			
the International Preliminary Examining Authority	other:			
The International Bureau of WIPO	Authorized officer			
34, chemin des Colombettes 1211 Geneva 20, Switzerland	Céline Faust			
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38			

#### **PCT**





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT) (51) International Patent Classification 7: (11) International Publication Number: WO 00/15266 A61K 49/04 **A3** (43) International Publication Date: 23 March 2000 (23.03.00) (21) International Application Number: PCT/EP99/06830 (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, (22) International Filing Date: 15 September 1999 (15.09.99) ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, (30) Priority Data: SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, 98117598.7 16 September 1998 (16.09.98) UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, EP MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, (71) Applicant (for all designated States except US): GOLDHAM CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, BIOGLAN PHARMA GMBH [DE/DE]; Am Wasserberg NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, 11, D-86441 Zusmarshausen (DE). GN, GW, ML, MR, NE, SN, TD, TG). (72) Inventors; and (75) Inventors/Applicants (for US only): FRANK, Artur [DE/DE]: Published Am Wasserberg 11, D-86441 Zusmarshausen (DE). GI-With international search report. ANETTINO, Andreina [IT/IT]; Via Francesco Sapori, 49, I-00143 Roma (IT). (88) Date of publication of the international search report: 25 May 2000 (25.05.00) (74) Agent: WIBBELMANN, Jobst; Wuesthoff & Wuesthoff, Schweigerstrasse 2, D-81541 München (DE).

(54) Title: RADIO-CONTRAST AGENTS

#### (57) Abstract

7

An imaging or contrast agent comprising a stereoisomer of a compound with at least one chiral centre, wherein said stereoisomer is in stereoisomeric excess and causes fewer adverse side effects on administration, or is less chemotoxic, than at least one other stereoisomer of said chiral compound.

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K49/04 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system to llowed by classification symbols) IPC 7 A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category \* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X FELDER E ET AL: "IOPAMIDOL" 1-8,12, 1 January 1988 (1988-01-01), ANALYTICAL PROFILES OF DRUG SUBSTANCES, VOL. 17, 13 PAGE(S) 115 - 154 XP000562617 the whole document X WO 97 02235 A (RECORDATI CHEM PHARM 1-8,12, ;TARQUINI ANTONIO (IT); DONNARUMMA MARIA 13 (IT)) 23 January 1997 (1997-01-23) the whole document X WO 98 34908 A (DESANTIS NICOLA : BRACCO INT 1-8,12, BV (NL)) 13 August 1998 (1998-08-13) 13 the whole document Further documents are listed in the continuation of box C. X X Patent family members are listed in annex. \* Special categories of cited documents : "T" later document published after the International filing date or priority date and not in conflict with the application but clied to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance Invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. \*O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 29 February 2000 15/03/2000 Name and mailing address of the ISA **Authorized officer** European Patent Office, P.B. 5818 Patentiaan 2 Tel. (+31-70) 340-3016 Fax: (+31-70) 340-3016

Form PCT/ISA/210 (second sheet) (July 1992)

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Veronese, A



		 9/06830
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAWSON, PETER ET AL.: "Isomeric Purity and Supersaturation of Iopamidol" BR. J. RADIOL., vol. 56, no. 670, 1983, pages 711-713, XP002096202 the whole document	1-14
X	PITRE D. ET AL.: "Development, Chemistry and Physical Properties of Iopamidol and its Analogs" INVESTIGATIVE RADIOLOGY, vol. 15, no. 6 Suppl., 1980, pages S301-S306, XP002096203 the whole document	1-14
X	WO 97 19705 A (ELMALEH DAVID R) 5 June 1997 (1997-06-05) the whole document	1-7
A	THE MERK LAORATORIES: "The Merk Index", MERK AND CO. INC., N.J. (U.S.A.) XP002131835 page 862 page 866-869	12

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on patent family members

Intri Paris Application No PCI/EP 99/06830

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9702235	A	23-01-1997	IT IT AU EP	MI951429 A MI952572 A 6516196 A 0842141 A	07-01-1997 06-06-1997 05-02-1997 20-05-1998
WO 9834908	A	13-08-1998	AU EP NO ZA	1455397 A 0966428 A 993851 A 9801070 A	26-08-1998 29-12-1999 10-08-1999 27-08-1998
WO 9719705	A	05-06-1997	CA EP	2238860 A 0869821 A	05-06-1997 14-10-1998

**PCT** 

	REC'D	27	DEC	2000	
1	MIDC	)		PCT	

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's	or ag	ent's file reference	<del></del>				<del></del>
EP-8324	_		FOR FURTHER AC	TION		of Transmittal of Internation nination Report (Form PCT	
Internation	al app	lication No.	International filing date (	day/month/yea	r) Prio	rity date (day/month/year)	
PCT/EPS	99/06	830	15/09/1999	16/09/1998			
Internation A61K49/		ent Classification (IPC) or na	ational classification and IPC				
Applicant GOLDHA	АМ В	IOGLAN PHARMA GI	MBH et al.				
		ational preliminary exam smitted to the applicant a	nination report has been according to Article 36.	prepared by	this Internatio	onal Preliminary Examir	ning Authority
2. This	REPO	ORT consists of a total of	6 sheets, including this	cover sheet	•		
b (:	een a see F	amended and are the ba	ed by ANNEXES, i.e. she sis for this report and/or 07 of the Administrative 1 sheets.	sheets conta	ining rectifica	tions made before this	nich have Authority
3. This r	eport	contains indications rela	ating to the following iten	ns:			
I	☒	Basis of the report					
11		Priority					
Ш	×		ppinion with regard to no	velty, inventi	ve step and in	ndustrial applicability	
IV	_	Lack of unity of invention					
V	×	Heasoned statement u citations and explanation	nder Article 35(2) with re ons suporting such state	egard to nove ment	elty, inventive	step or industrial applic	ability;
VI		Certain documents cite	· -				
VII		Certain defects in the in	nternational application				
VIII		Certain observations of	n the international applic	ation			
<u></u>							
Date of sub	missio	on of the demand		Date of comp	letion of this rep	port	
10/04/20	00			21.12.2000			
	exam	g address of the international ining authority:	ıl	Authorized o	ficer		SPECT & SOVES MIEN SWAP
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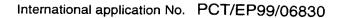


1.	res <sub>i</sub> the	ponse to an invitatio	awn on the basis of (substitute n under Article 14 are referred to not contain amendments (Rule	to in this repo	rt as "originally filed" a	to the receiving Office in and are not annexed to
	1-5	:	as originally filed			
	Cla	ims, No.:				
	1-4	i	as received on	10/04/2000	with letter of	10/04/2000
2.	lang	guage in which the in	lage, all the elements marked attenuational application was filed	d, unless othe	erwise indicated under	this item.
	ine	se elements were av	ailable or furnished to this Auth	nority in the to	ollowing language: ,	which is:
		the language of a tr	anslation furnished for the purp	oses of the ir	nternational search (ui	nder Rule 23.1(b)).
		the language of pub	dication of the international app	lication (unde	er Rule 48.3(b)).	
		the language of a tr 55.2 and/or 55.3).	anslation furnished for the purp	oses of interr	national preliminary ex	camination (under Rule
3.			eotide and/or amino acid sequexamination was carried out or			I application, the
		contained in the inte	ernational application in written	form.		
		filed together with th	ne international application in co	omputer read	able form.	
		furnished subseque	ntly to this Authority in written f	orm.		
		furnished subseque	ntly to this Authority in compute	er readable fo	rm.	
		The statement that the international app	the subsequently furnished writ blication as filed has been furni	tten sequence shed.	e listing does not go be	eyond the disclosure in
		The statement that the listing has been furn	the information recorded in comished.	nputer readab	ele form is identical to	the written sequence
4.	The	amendments have r	resulted in the cancellation of:			
		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			
5.		This report has been considered to go be	n established as if (some of) the yond the disclosure as filed (Ru	e amendment ule 70.2(c)):	s had not been made	, since they have been



(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6.	Add	ditional observations, if n	ecessa	ry:	
111.	. No	n-establishment of opi	nion wi	th regard	d to novelty, inventive step and industrial applicability
	The	questions whether the	claimed	invention	n appears to be novel, to involve an inventive step (to be non-
		the entire international	applicat	ion.	
	×	claims Nos. 3.			
be	caus	se:			
	Ø	the said international apmatter which does not resee separate sheet	oplicatio require a	n, or the a	e said claims Nos. 3, in respect of i.a. relate to the following subject ational preliminary examination ( <i>specify</i> ):
		the description, claims of that no meaningful opin			licate particular elements below) or said claims Nos. are so unclear med (specify):
		the claims, or said claim could be formed.	ns Nos.	are so in	nadequately supported by the description that no meaningful opinion
		no international search	report h	as been	established for the said claims Nos
2.	and	eaningful international p /or amino acid sequence ructions:	relimina e listing	ry examin to comply	ination report cannot be carried out due to the failure of the nucleotid y with the standard provided for in Annex C of the Administrative
		the written form has not	been fu	urnished o	or does not comply with the standard.
		the computer readable t	form ha	s not bee	en furnished or does not comply with the standard.
<b>/</b> .	Rea cita	soned statement unde tions and explanations	r Article	e 35(2) w rting suc	vith regard to novelty, inventive step or industrial applicability; ch statement
١.	Stat	ement			
	Nov	elty (N)	Yes: No:	Claims Claims	
	Inve	entive step (IS)	Yes: No:	Claims Claims	
	Indu	strial applicability (IA)	Yes:	Claims	





No: Claims 3

2. Citations and explanations see separate sheet

#### Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 3 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

#### Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DAWSON, PETER ET AL.: 'Isomeric Purity and Supersaturation of Iopamidol' BR. J. RADIOL., vol. 56, no. 670, 1983, pages 711-713

D2: FELDER E ET AL: 'IOPAMIDOL' 1 January 1988 (1988-01-01), ANALYTICAL PROFILES OF DRUG SUBSTANCES, VOL. 17, PAGE(S) 115 - 154

#### Novelty and Inventive Step (Art. 33(2) and 33(3) PCT).

D1 discloses that the solubility of iopamidol probably depends on the isomeric purity of the preparation, being for instance the solubility of the L(S)-form higher than the racemate's one. A typical D(R)-isomer concentration is 1.6% (see page 713, left column, second paragraph). The document neither mentions a solution of iopamidol with a concentration of R-iopamidol higher than 50% nor discloses the relationship between R-iopamidol and fewer adverse side effects on administration (chemotoxicity).

According to the remaining prior art and as stated in the description of the present application iopamidol is only available in the S-form (98.9% of L(S)-form and 1.62 % of D(R)-form) (see D2, 3.3.1 optical rotation).

Thus, the subject-matter of claims 1-4 appears to be novel.

However, the present invention does not involve an inventive step. The technical problem to be solved in view of the prior art which uses S (L)-iopamidol as an imaging or contrast agent is to reduce the chemotoxicity of the compound. The solution of choosing the R (D)-isomer is obvious taking into accoount that biological systems depen on specific detailed recognition of molecules involving differentiation between quiral forms and that all amino acids in the proteins have the L-configuration. Therefore, if the objective is to reduce chemotoxicity, namely to avoid interaction with molecules as proteins in the body, it is obvious to use the R (D)-isomer of the compound.

#### Industrial Applicability (Art. 33(4) PCT).

For the assessment of the present claim 3 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### Amended claims

- 1. An imaging or contrast agent comprising iopamidol characterised in that said agent comprises greater than 50 % of R-iopamidol.
- 2. The imaging or contrast agent as claimed in claim 1, wherein said agent comprises greater than 80 % R-iopamidol.
- 3. A use of R-iopamidol in an imaging or contrast agent wherein said agent causes fewer adverse side effects on administration.
- 4. A use of R-iopamidol to produce an imaging or contrast agent being less chemotoxic.

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# PATENT COOPERATION TREATY





# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's	or ag	ent's file reference			Con Notific	ation of Transmitted of Lat.		
EP-8324	4/PC	T .	FOR FURTHER ACTION  See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)					
Internation	al app	lication No.	International filing date (d	ay/month/	'year)	Priority date (day/month	/year)	
PCT/EP			15/09/1999			16/09/1998		
A61K49/		ent Classification (IPC) or na	tional classification and IPC					
Applicant GOLDH	AM B	IOGLAN PHARMA GN	1BH et al.					
1. This and is	ntern s tran	ational preliminary exams	ination report has been p according to Article 36.	repared	by this Inte	rnational Preliminary E	xamining Authority	
2. This	REPO	ORT consists of a total of	7 sheets, including this	cover sh	eet.			
b	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).							
These	ann	exes consist of a total of	1 sheets.					
3. This r	eport	contains indications rela	ting to the following items	s: <b>C</b>				
1	$\boxtimes$	Basis of the report						
II		Priority				RSION		
Ш	$\boxtimes$	Non-establishment of o	inion with regard to novelty, inventive step and industrial applicability					
IV		Lack of unity of inventio	n	, , , , , , , , , , , , , , , , , , , ,				
V	$\boxtimes$	Reasoned statement un citations and explanatio	der Article 35(2) with reg	ard to no	ovelty, inver	ntive step or industrial a	applicability;	
VI		Certain documents cite	d					
VII		Certain defects in the in	ternational application					
VIII	×	Certain observations on	the international applica	tion				
Date of sub	missio	n of the demand		Date of co	mpletion of t	his report		
10/04/200	00					25. 01. <b>01</b>		
		address of the international ning authority:	,	Authorized	d officer	<del> · </del>	SHOP LECKES PATERIUM	
<b>)</b>	Euro D-80 Tel	pean Patent Office 298 Munich +49 89 2399 - 0 Tx: 523656 +49 89 2399 - 4465	epmu d	Simm, N			A THE WAY AS BOARD SAY WAY	
	Telephone No. +49 89 2399 7411					3040.2		



l. Bas	is 1	i th	r	port
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1.	res the	sponse to an invitatio	rawn on the basis of (substitu on under Article 14 are referre o not contain amendments (Fi	ed to in this repo	ort as "originally file	hed to the receiving Office in ed" and are not annexed to
	1-5	5	as originally filed			
	Cla	nims, No.:				
	1-4		as received on	10/04/2000	with letter of	10/04/2000
2.	lan	guage in which the in	uage, all the elements marke nternational application was f vailable or furnished to this A	iled, unless othe	erwise indicated u	nder this item.
		the language of pul	ranslation furnished for the poolication of the international a	application (unde	er Rule 48.3(b)).	, ,
3.	Wit	h regard to any <b>nucl</b> rnational preliminary	eotide and/or amino acid so examination was carried out	equence disclost t on the basis of	sed in the internat the sequence list	ional application, the ing:
		contained in the int	ernational application in writte	en form.		
		filed together with t	he international application in	computer read	able form.	
		furnished subseque	ently to this Authority in writte	n form.		
		furnished subseque	ently to this Authority in comp	uter readable fo	rm.	
		The statement that the international ap	the subsequently furnished v plication as filed has been ful	vritten sequence rnished.	e listing does not o	go beyond the disclosure in
		The statement that listing has been furn	the information recorded in c nished.	omputer readab	ole form is identica	al to the written sequence
4.	The	amendments have	resulted in the cancellation of	f:		
		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			
5.		This report has bee considered to go be	n established as if (some of) eyond the disclosure as filed (	the amendment (Rule 70.2(c)):	ts had not been m	ade, since they have been



(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6.	Add	ditional observations, if r	necessa	ıry:	
111.	. No	n-establishment of opi	nion wi	th regard	d to novelty, inventive step and industrial applicability
1.	The obv	e questions whether the vious), or to be industrial	claimed ly applic	l inventior cable have	n appears to be novel, to involve an inventive step (to be non- re not been examined in respect of:
		the entire international	applica	tion.	
	×	claims Nos. 3.			
be	caus	se:			
	×	the said international apmatter which does not see separate sheet	oplicatio require	on, or the an interna	said claims Nos. 3, in respect of i.a. relate to the following subject ational preliminary examination ( <i>specify</i> ):
		the description, claims that no meaningful opin	or draw iion cou	ings ( <i>indi</i> ld be forn	icate particular elements below) or said claims Nos. are so unclear med (specify):
		the claims, or said clain could be formed.	ns Nos.	are so ir	nadequately supported by the description that no meaningful opinion
		no international search	report h	nas been	established for the said claims Nos
2.	and	eaningful international p /or amino acid sequence ructions:	relimina listing	ary exami to comply	ination report cannot be carried out due to the failure of the nucleotide y with the standard provided for in Annex C of the Administrative
		the written form has not	been f	urnished (	or does not comply with the standard.
		the computer readable	form ha	s not bee	en furnished or does not comply with the standard.
V.	Rea cita	soned statement unde tions and explanations	r Articl	e 35(2) w erting suc	vith regard to novelty, inventive step or industrial applicability;
1.	Stat	ement			
	Nov	elty (N)	Yes: No:	Claims Claims	
	Inve	ntive step (IS)	Yes: No:	Claims Claims	1-2
	Indu	strial applicability (IA)	Yes:	Claims	1.2.4





No: Claims 3

2. Citations and explanations see separate sheet

#### VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

#### R Item I

#### Basis of the report

D1: DAWSON, PETER ET AL.: 'Isomeric Purity and Supersaturation of Iopamidol' BR. J. RADIOL., vol. 56, no. 670, 1983, pages 711-713

D2: FELDER E ET AL: 'IOPAMIDOL' 1 January 1988 (1988-01-01), ANALYTICAL PROFILES OF DRUG SUBSTANCES, VOL. 17, PAGE(S) 115 - 154

#### Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 3 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

#### Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Art. 33(2) PCT).

D1 discloses that the solubility of iopamidol probably depends on the isomeric purity of the preparation, being for instance the solubility of the L(S)-form higher as the racemate's one. A typical D(R)-isomer concentration is 1.6% (see page 713, left column, second paragraph). The document neither mentions a solution of iopamidol with a concentration of R-iopamidol higher than 50% nor discloses the relationship between R-iopamidol and fewer adverse side effects on administration (chemotoxicity).

According to the remaining prior art and as stated in the description of the present application iopamidol is only available in the S-form (98.9% of L(S)-form and 1.62 % of D(R)-form) (see D2, 3.3.1 optical rotation). Thus, the subject-matter of claims 1-2 appears to be novel.

However, the subject-matter of claims 3 and 4 which refers to the use of R-iopamidol without indicating the % is not considered to be novel because the contrast agents known from the prior art comprise R-iopamidol (1.6 %) and the expressions "being less chemotoxic" and "wherein said agent causes fewer adverse side effects on administration" have no limiting effect over the scope of these claims (see Item VIII).

#### Inventive Step (Art. 33(3) PCT).

The present invention differs from the cited prior art in that the contrast agent comprises more than 50% R-iopamidol. The technical effect is that the contrast agent is less chemotoxic. The technical problem solved by the present application is then to provide a contrast agent based on iopamidol which is less chemotoxic. The solution given in the present invention, a contrast agent comprising more than 50% R-iopamidol is neither disclosed nor merely suggested in the cited prior art. Thus, the subject-matter of claims 1-2 appears to be inventive.

#### Industrial Applicability (Art. 33(4) PCT).

For the assessment of the present claim 3 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### <u>Item VIII</u>

Certain observations on the international application

International application No. PCT/EP99/06830

Claims 3 and 4 appear to lack an essential feature according to the description (see page 2, lines 25-30) and the subject-matter of claim 1, namely that the contrast agent comprises more that 50% of R-iopamidol (Art. 6 and PCT Guidelines III-4.3).

Moreover, the expressions "wherein said agent causes fewer adverse side effects on administration" in claim 3 and "being less chemotoxic" in claim 4 express just a result to be achieved and as such render the scope of these claims unclear (Art. 6 and PCT Guidelines III-4).

In claim 1 it appears that the expression "greater than" should read "more than".

From the INTERNATIONAL PRELIMINATE EXAMINING AUTHORITY Wibbelmann, Jobst WUESTHOFF & WUESTHOFF NOTIFICATION OF TRANSMITTAL OF Schweigerstrasse 2 THE INTERNATIONAL PRELIMINARY 81541 München **EXAMINATION REPORT ALLEMAGNE** (PCT Rule 71.1) 26 JAN. 2001 Date of mailing 'day/month/year) 25. 01. 01 Applicant's or agent's file reference EP-83244/PCT IMPORTANT NOTIFICATION International filing date (day/month/year) International application No. Priority date (day/month/year) PCT/EP99/06830 15/09/1999 16/09/1998 Applicant GOLDHAM BIOGLAN PHARMA GMBH et al.

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

Authorized officer

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 D-80298 Munich
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Fax: +49 89 2399 - 4465

Senkel, H

Tel.+49 89 2399-8071



## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTUER AG	TION	ation of Transmittal of International				
EP-83244/PCT	FOR FURTHER AC	Preliminary	Examination Report (Form PCT/IPEA/416)				
International application No.	International filing date (d	lay/month/year)	Priority date (day/month/year)				
PCT/EP99/06830	15/09/1999		16/09/1998				
International Patent Classification (IPC) or national classification and IPC A61K49/00							
Applicant		. •					
GOLDHAM BIOGLAN PHARMA GM	IBH et al.						
<ol> <li>This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</li> </ol>							
2. This REPORT consists of a total of	7 sheets, including this	cover sheet.					
This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  These annexes consist of a total of 1 sheets.							
3. This report contains indications rela	ting to the following item	ns:					
I ⊠ Basis of the report			·				
II □ Priority							
III 🖾 Non-establishment of o	pinion with regard to nov	elty, inventive step	and industrial applicability				
IV							
V 🛛 Reasoned statement ur citations and explanatio	ider Article 35(2) with re- ns suporting such stater	gard to novelty, inve ment	entive step or industrial applicability;				
VI 🗆 Certain documents cite			•				
	VII						
VIII 🛛 Certain observations on	the international applica	ation					
Date of submission of the demand		Date of completion of	this report				

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Telephone No. +49 89 2399 7411

25. 01. 01

10/04/2000

International application No. PCT/EP99/06830

#### I. Basis of the report

1.	res the	ponse to an invitation	rawn on the basis of (so on under Article 14 are to o not contain amendme	referred to in this rep	ort as "originally file	hed to the receiving ed" and are not and	g Office in nexed to
	1-5		as originally filed				
	Cla	ims, No.:					
	1-4		as received on	10/04/2000	) with letter of	10/04/2000	
2.			uage, all the elements nternational application				in the
	The	ese elements were a	vailable or furnished to	this Authority in the	following language	: , which is:	
		the language of a t	ranslation furnished for	the purposes of the	international searc	h (under Rule 23.1	(b)).
		the language of pul	blication of the internat	ional application (un	der Rule 48.3(b)).		
		the language of a to 55.2 and/or 55.3).	ranslation furnished for	the purposes of inte	ernational prelimina	ry examination (un	der Rule
3.			eotide and/or amino a examination was carr				ne
		contained in the int	ernational application is	n written form.	·		
			he international applica		idable form.		
		furnished subseque	ently to this Authority in	written form.			
		furnished subseque	ently to this Authority in	computer readable	form.		
			the subsequently furni plication as filed has b		ce listing does not	go beyond the disc	losure in
		The statement that listing has been fur	the information recordenished.	ed in computer read	able form is identica	al to the written sec	luence
4.	The	amendments have	resulted in the cancella	ation of:	* .		
		the description,	pages:	·			. •
		the claims,	Nos.:	•	. •	•	
		the drawings,	sheets:				
5.			en established as if (sor eyond the disclosure as			nade, since they ha	ve been



(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6.	. Add	ditional observations, if r	necessa	ry:					<b>:</b>		
						•					
III	. No	n-establishment of opi	nion wi	th regard	to nove	elty, inve	ntive step	and ind	ustrial ap	plicability	y
1.		e questions whether the vious), or to be industrial							nventive s	tep (to be	non-
		the entire international	applicat	ion.				•	•		• .
	×	claims Nos. 3.					٠				
be	ecaus	se:	,							-	
	×	the said international a matter which does not see separate sheet								ne followir	ng subject
		the description, claims that no meaningful opin					ements belo	ow) or sa	id claims	Nos. are	so unclear
		the claims, or said clair could be formed.	ns Nos.	are so ir	adequa	tely suppo	orted by th	e descrip	otion that r	no meanir	ngful opinion
		no international search	report h	nas been	establis	ned for th	e said clair	ns Nos.		•	
2.	and	neaningful international p lor amino acid sequence ructions:									
		the written form has no	t been f	urnished (	or does	not comp	ly with the	standard	<b>.</b>		
		the computer readable					-			ard.	
٧.	Rea	soned statement unde tions and explanations	er Articl	e 35(2) w orting suc	ith rega th state	rd to nov	velty, inve	ntive ste	ep or indu	ıstrial ap <sub>l</sub>	plicability;
1.	Stat	tement						7			
-	Nov	relty (N)	Yes: No:	Claims Claims							
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-2						
	Indi	strial applicability (IA)	Yes:	Claims	1.2.4			•			

International application No. PCT/EP99/06830

No: Claims 3

2. Citations and explanations see separate sheet

#### VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

See separate sheet

#### Re Item I

#### Basis of the report

D1: DAWSON, PETER ET AL.: 'Isomeric Purity and Supersaturation of Iopamidol' BR. J. RADIOL., vol. 56, no. 670, 1983, pages 711-713

D2: FELDER E ET AL: 'IOPAMIDOL' 1 January 1988 (1988-01-01), ANALYTICAL PROFILES OF DRUG SUBSTANCES, VOL. 17, PAGE(S) 115 - 154

#### Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 3 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

#### Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Art. 33(2) PCT).

D1 discloses that the solubility of iopamidol probably depends on the isomeric purity of the preparation, being for instance the solubility of the L(S)-form higher as the racemate's one. A typical D(R)-isomer concentration is 1.6% (see page 713, left column, second paragraph). The document neither mentions a solution of iopamidol with a concentration of R-iopamidol higher than 50% nor discloses the relationship between R-iopamidol and fewer adverse side effects on administration (chemotoxicity).

According to the remaining prior art and as stated in the description of the present application iopamidol is only available in the S-form (98.9% of L(S)-form and 1.62 % of

# INTERNATIONAL PR **EXAMINATION REPORT - SEPARATE SHEET**

D(R)-form) (see D2, 3.3.1 optical rotation). Thus, the subject-matter of claims 1-2 appears to be novel.

However, the subject-matter of claims 3 and 4 which refers to the use of R-iopamidol without indicating the % is not considered to be novel because the contrast agents known from the prior art comprise R-iopamidol (1.6 %) and the expressions "being less chemotoxic" and "wherein said agent causes fewer adverse side effects on administration" have no limiting effect over the scope of these claims (see Item VIII).

#### Inventive Step (Art. 33(3) PCT).

The present invention differs from the cited prior art in that the contrast agent comprises more than 50% R-iopamidol. The technical effect is that the contrast agent is less chemotoxic. The technical problem solved by the present application is then to provide a contrast agent based on iopamidol which is less chemotoxic. The solution given in the present invention, a contrast agent comprising more than 50% R-iopamidol is neither disclosed nor merely suggested in the cited prior art. Thus, the subject-matter of claims 1-2 appears to be inventive.

#### Industrial Applicability (Art. 33(4) PCT).

For the assessment of the present claim 3 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

#### Item VIII

Certain observations on the international application

Claims 3 and 4 appear to lack an essential feature according to the description (see page 2, lines 25-30) and the subject-matter of claim 1, namely that the contrast agent comprises more that 50% of R-iopamidol (Art. 6 and PCT Guidelines III-4.3).

Moreover, the expressions "wherein said agent causes fewer adverse side effects on administration" in claim 3 and "being less chemotoxic" in claim 4 express just a result to be achieved and as such render the scope of these claims unclear (Art. 6 and PCT Guidelines III-4).

In claim 1 it appears that the expression "greater than" should read "more than".

#### Amended claims

- 1. An imaging or contrast agent comprising iopamidol characterised in that said agent comprises greater than 50 % of R-iopamidol.
- 2. The imaging or contrast agent as claimed in claim 1, wherein said agent comprises greater than 80 % R-iopamidol.
- 3. A use of R-iopamidol in an imaging or contrast agent wherein said agent causes fewer adverse side effects on administration.
- 4. A use of R-iopamidol to produce an imaging or contrast agent being less chemotoxic.

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'(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference EP-83244/PCT		of Transmittal of International Search Report 220) as well as, where applicable, Item 5 below.						
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)						
PCT/EP 99/06830 15/09/1999 16/09/1998								
Applicant GOLDHAM BIOGLAN PHARMA GM	BH et al.							
This international Search Report has bee according to Article 18. A copy is being tr	n prepared by this international Searching Aut anamitted to the international Bureau.	hority and is transmitted to the applicant						
This international Search Report consists  It is also accompanied by	of a total of 3 sheets.  va copy of each prior art document cited in this	report.						
	international search was carried out on the ba less otherwise indicated under this item.	sis of the international application in the						
the international search w Authority (Rule 23.1(b)).	vas carried out on the basis of a translation of	the international application furnished to this						
was carried out on the basis of the contained in the internation of the contained out on the basis of the contained in the basis of the contained out on the basis of the contained in the basis of the contained out on the basis of the contained in the basis of the contained in the basis of the contained in the later of the contained in the contained in the later of the later of the contained in the later of the contained in the later of the	b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:  contained in the international application in written form.  filled together with the international application in computer readable form.  furnished subsequently to this Authority in written form.							
furnished subsequently to	this Authority in computer readble form.							
	bsequently furnished written sequence listing on the sequence is the sequence	loes not go beyond the disclosure in the						
the statement that the infe	ormation recorded in computer readable form	is identical to the written sequence listing has been						
물	ind unsearchable (See Box I).							
3. Unity of invention is lac	iding (see box ii).							
4. With regard to the title,								
the text is approved as su	•							
The text has been estable	shed by this Authority to read as follows:							
5. With regard to the abstract,								
the text is approved as su the text has been establic within one month from the	• • • • • • • • • • • • • • • • • • • •	ity as it appears in Box III. The applicant may, port, submit comments to this Authority.						
6. The figure of the drawings to be pub								
as suggested by the appl	•	None of the figures.						
because the applicant fall	ed to suggest a figure.	<del></del>						
because this figure better	characterizes the Invention.							

thermational Application No T/EP 99/06830

A T F	CLA	881FIC 7	ATION A61	10F (49	SUB. /04	ECT	i Ar

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7-A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Bectronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUM	DOCUMENTS CONSIDERED TO BE RELEVANT							
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.						
х	FELDER E ET AL: "IOPAMIDOL"  1 January 1988 (1988-01-01) , ANALYTICAL PROFILES OF DRUG SUBSTANCES, VOL. 17, PAGE(S) 115 - 154 XP000562617 the whole document	1-8,12, 13						
x	WO 97 02235 A (RECORDATI CHEM PHARM; TARQUINI ANTONIO (IT); DONNARUMMA MARIA (IT)) 23 January 1997 (1997-01-23) the whole document	1-8,12, 13						
X	WO 98 34908 A (DESANTIS NICOLA ;BRACCO INT BV (NL)) 13 August 1998 (1998-08-13) the whole document	1-8,12, 13						

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.		
Special categories of cited documents:  "A" document defining the general state of the art which is not considered to be of particular relevance  "E" earlier document but published on or after the international filing date  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  "O" document referring to an oral disclosure, use, exhibition or other means  "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report		
29 February 2000	15/03/2000		
Name and mailing address of the ISA	Authorized officer		
European Patent Office, P.B. 5816 Patentlaan 2 NL – 2280 HV Rijawljk Tel. (+31–70) 340–2040, Tx. 31 661 epo ni, Fac (+31–70) 340–3016	Veronese, A		

International Application No CT/EP 99/06830

	ation) DOCUMENTS COLUMED TO BE RELEVANT			
ategory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	DAWSON, PETER ET AL.: "Isomeric Purity and Supersaturation of Iopamidol" BR. J. RADIOL., vol. 56, no. 670, 1983, pages 711-713, XP002096202 the whole document	1-14		
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